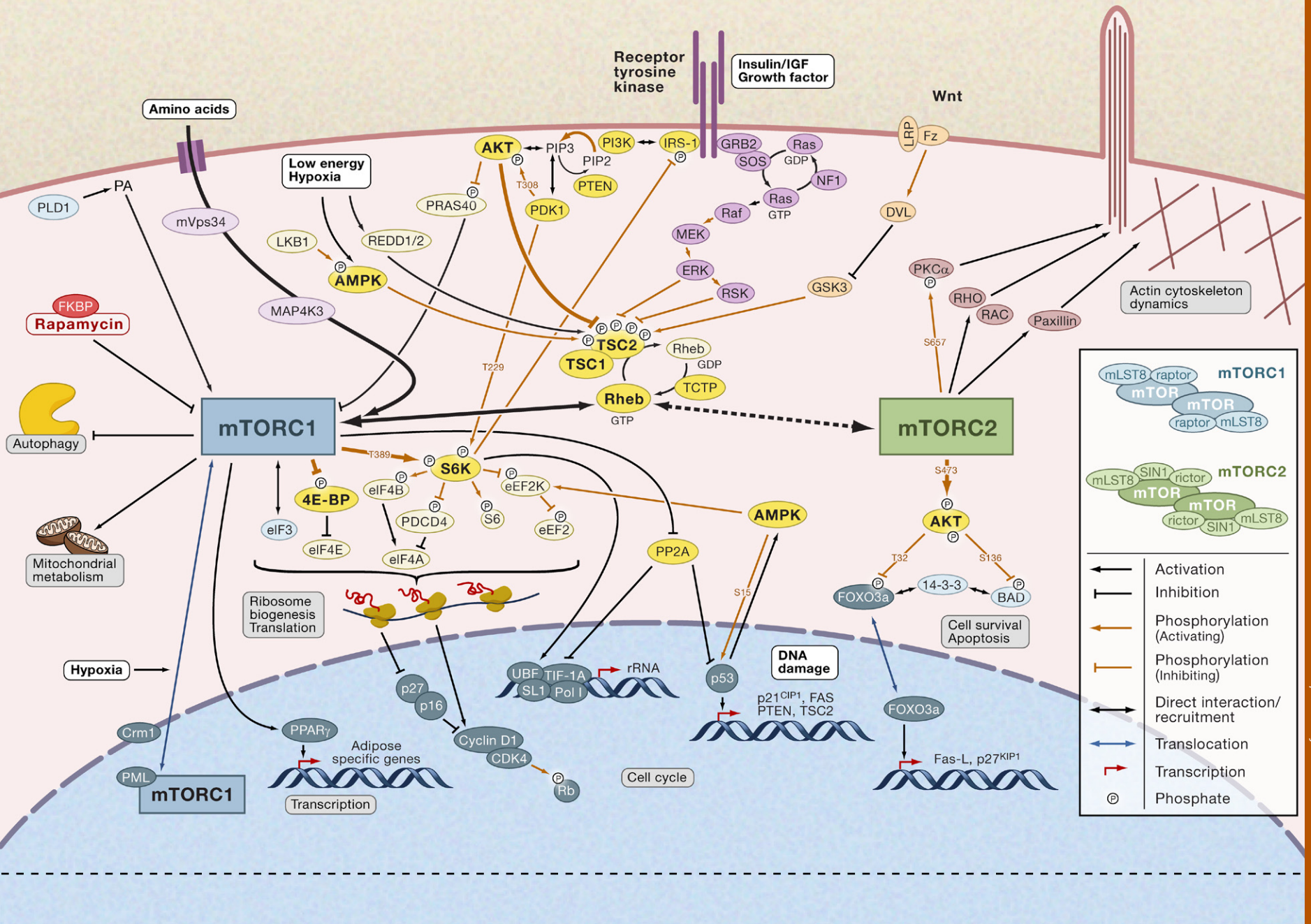
SnapShot: mTOR Signaling

Alexandre Soulard and Michael N. Hall
Biozentrum, University of Basel, CH-4056 Basel, Switzerland



434 Cell 129, April 20, 2007 ©2007 Elsevier Inc. DOI 10.1016/j.cell.2007.04.010

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Cell

mTOR (mammalian Target of Rapamycin) integrates three major inputs—nutrients (amino acids), growth factors (insulin), and cellular energy status—to control several catabolic and anabolic processes that collectively determine cell growth and metabolism. mTOR forms two structurally and functionally distinct multiprotein complexes, mTORC1 and mTORC2, which correspond to two major branches within the overall signaling network. Both mTORC1 and mTORC2 are atypical serine/threonine kinases. The main components of the network other than the mTORCs are depicted in bright yellow. In response to growth factors, AKT phosphorylates and inactivates TSC1-TSC2 (a heterodimeric GTPase-activating protein), allowing GTP-bound Rheb (a Ras-like GTPase) to activate mTORC1 and possibly mTORC2. Low energy (cellular energy status) inhibits mTORC by activating AMPK, which phosphorylates and activates TSC1-TSC2. The pathway by which amino acids, leucine in particular, activate mTORC1 is poorly understood. mTORC1 controls protein synthesis by phosphorylating and inactivating the translational inhibitor 4E-BP and by phosphorylating and activating S6 kinase (S6K). S6K, in addition to phosphorylating various translational targets, also phosphorylates and inhibits insulin receptor substrate 1 (IRS-1) as part of a negative feedback loop that attenuates insulin signaling. mTORC2 promotes cell survival through direct phosphorylation of serine 473 in the hydrophobic motif of AKT. The immunosuppressant rapamycin in complex with FKBP binds and inhibits mTORC1 but not mTORC2. mTOR signaling is deregulated in many diseases including cancer and metabolic disorders. mTOR also mediates nutrient-related processes such as appetite control and aging.

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  DOI 10.1016/j.cell.2007.04.010